

Serial No. 10/009,972
Reply to Office Action of December 19, 2003

AMENDMENTS TO THE DRAWING

Attached hereto is a replacement drawing of Figure 2.

Attachment

37 CFR §1.131 Declaration

REMARKS

Applicant notes with appreciation the well-reasoned and thorough final Office Action mailed 19 December 2003. This amendment is submitted to be fully responsive thereto. With this amendment, claims 1, 9, 17, 20 and 21 have been amended. Claims 3, 4, 10, 11 and 19 have been canceled. New claims 24-26 have been added. The potential allowability of claims 19-21 if written in independent form is noted with appreciation. A revised declaration is submitted herewith in compliance with 37 CFR §1.131. Support for the amendment to the specification is found in the PCT amendment filed under Articles 66.3 and 66.8 of record in a priority application predating the filing of the United States national phase application. Support for the amendments to claims 1, 9, 17, 20 and 21 and new claims 24 and 25 is found in the claims as filed. Support for new claim 26 is found in the specification at page 14, lines 3 and 4. As such, it is submitted that no new matter has been added by way of this amendment.

Remarks Regarding Priority

In view of Applicant's belief of allowability as to all the pending claims pending entry of this amendment, Applicant reserves the right to make of record additional comments in support of the assertion that Applicant was in possession of the claimed subject matter upon the date of provisional application and that those applications provided adequate written description to place the claimed invention in the hands of the public.

**Remarks Directed to Rejection of
Claims 16 and 23 under 35 U.S.C. §112, First Paragraph**

The rejection of claims 16 and 23 under 35 U.S.C. §112, first paragraph, is respectfully submitted to be improper in light of the PCT amendment of record affording support for these claims. As this amendment was made prior to filing of the U.S. national phase application, this subject matter is part of the application as filed. The specification has been amended based on this PCT amendment to provide explicit support for claims 16 and 23.

In view of the above amendment and remarks, the rejection of claims 16 and 23 under 35 U.S.C. §112, first paragraph, is hereby solicited.

**Remarks Directed to Rejection of Claims 1-3,
5, 9, 10 and 13-15 under 35 U.S.C. §102(e)**

Applicant submits herewith a revised declaration under 37 CFR §1.131 effective to show Applicant's invention of vectors per the rejected claims, antecedent to the priority date claimed by Wechsler et al. The declaration shows evidence of Applicant's invention of vectors described in the rejected claims under §102(e) as cited above, prior to the priority date claimed by Wechsler et al. Specifically, notarized copies of dated laboratory notebook pages already of record show that IL-12 expressing HSV vector as described in independent claims 1 and 9 was in Applicant's hands as of August 21, 1998. Further, notarized copies of dated laboratory notebook pages already of record are submitted to show a GM-CSV expressing HSV vector per independent claims 1 and 9 at least as of March 24, 1999. Applicant submits that the appended declaration is evidence of prior invention as compared to the priority date claimed by the Wechsler et al. application. Applicant reserves the right to submit further factual evidence showing earlier dates relating to the present invention.

In view of the evidence of record and the attached declaration, it is submitted that claims 1-3, 5, 9, 10 and 13-15 that stand rejected under 35 U.S.C. §102(e) as anticipated by Wechsler et al. is no longer proper and it is respectfully requested that it be withdrawn.

**Remarks Directed to Rejection of Claims 17, 18 and 22
under 35 U.S.C. §§102(a), (b) and (e) as Anticipated by DeLuca**

In light of the objected-to subject matter of claim 19 being present in independent claim 17 in current form, it is now believed that the rejection of independent claim 17, as well as dependent claims 18 and 22 therefrom, has been overcome. Withdrawal of the rejection as to claims 17, 18 and 22 under 35 U.S.C. §§102(a), (b) and (e) as anticipated by DeLuca is no longer proper and it is respectfully requested that it be withdrawn.

**Remarks Directed to Rejection of Claims 1, 2, 9, 15 and 16
under 35 U.S.C. §102(e) as Anticipated by Boursnell et al.**

Claims 1 and 9 have been amended to recite aneurovirulency. As this limitation is nowhere taught in Boursnell et al., it is now submitted that all the pending claims are patentable over Boursnell et al.

In light of the above amendments and remarks, withdrawal of the rejection as to claims 1, 2, 9, 15 and 16 under 35 U.S.C. §102(e) as anticipated by Boursnell et al. is solicited.

**Remarks Directed to Rejection of Claims 1, 2, 9, 15 and 16
under 35 U.S.C. §102(b) as Anticipated by Inglis et al.**

Claims 1 and 9 have been amended to recite aneurovirulency. As this limitation is nowhere taught in Inglis et al., it is now submitted that all the pending claims are patentable over Inglis et al.

In light of the above amendments and remarks, withdrawal of the rejection as to claims 1, 2, 9, 15 and 16 under 35 U.S.C. §102(e) as anticipated by Inglis et al. is solicited.

**Remarks Directed to Rejection of Claims 1, 2, 9 and 15
under 35 U.S.C. §102(a) as Anticipated by Todryk et al.**

Claims 1 and 9 have been amended to recite aneurovirulency. As this limitation is nowhere taught in Todryk et al., it is now submitted that all the pending claims are patentable over Todryk et al.

In light of the above amendments and remarks, withdrawal of the rejection as to claims 1, 2, 9, 15 and 16 under 35 U.S.C. §102(e) as anticipated by Todryk et al. is solicited.

**Remarks Directed to Rejection of Claims 9, 12 and 13 under
35 U.S.C. §103(a) over Wechsler et al. in View of Toda et al.**

In addition to Applicant's reliance on the supplemental declaration provided under 37 CFR §1.131 provided as part of this amendment, Applicant notes that the prior art combination of Wechsler et al. in view of Toda et al. teaches away from the claimed invention. Specifically, Wechsler et al. at paragraph [0023] identifies the need satisfied by the invention of Wechsler et al. as producing a virulence impaired HSV-1 derived cancer therapy vector and capable of spontaneous reactivation. Applicant submits that to modify the teaching of Wechsler et al. in view of Toda to yield the claimed invention would be contrary to the teachings of Wechsler et al.

In light of the supplemental declaration under 37 CFR §1.131 or the above amendment and remarks, it is now believed that the rejection of claims 9, 12 and 13 under 35 U.S.C. §103(a) over Wechsler et al. in view of Toda et al. is no longer proper and it is respectfully requested that it be withdrawn.

**Remarks Directed to Rejection of Claims 1, 2, 5-9 and 12-16 under
35 U.S.C. §103(a) over Andreansky et al. in View of Toda et al.**

In the outstanding final Office Action, this rejection has been refined to state “Toda teaches that expression of IL-12 was superior to GM-CSF (page 4462, bottom of col. 2). Andreansky omitted IL-12 from the list, and Toda clearly demonstrates why IL-12 would have been an obvious alternative to the cytokines listed by Andreansky, such as GM-CSF.” (Paper No. 20031202, page 9, paragraph 1).

Applicant submits that statements of obviousness to attempt the substitution of IL-12 per Toda for the cytokines of Andreansky ignore the technical complexities inherent in the prior art reference combination. As Toda at page 4462, bottom of column 2, states that intra-tumoral inoculation of GM-CSF-expressing HSV vectors had only limited anti-tumoral efficacy, the prior art reference combination of Andreansky and Toda is inapplicable to new claims 24 and 25 on the basis that Toda teaches away from the subject matter of these claims.

With respect to claims 1, 2, 5-9 and 12-16, Andreansky teaches a vector containing a gene for IL-4. IL-4 is a 20 kD cytokine that stimulates resting B cells, activates macrophages, and otherwise functions as an autocrine growth factor for T-cells to induce differentiation of cytotoxic lymphocytes. Andreansky also teaches a vector containing a gene for IL-10, which is a 39 kD homodimer known to generally down regulate cytokine expression and decrease inflammatory response.

In contrast to the cytokines taught in Andreansky, IL-12 is a **heterodimeric** cytokine composed of p35 and p40 subunits. The prior art reference combination is used to create an obvious-to-try type rejection. However, substitution of the genes for IL-12 for those of either IL-4 or IL-10 requires the expression of two therapeutic anti-tumor genes, namely the two

separate subunits that make up the IL-12 protein, in contrast to the expression of single genes for IL-4 or IL-10 per Andreansky. Additionally, expression of the IL-12 subunits must then undergo assembly to form the functional, biologically active IL-12 protein. Providing a vector expressing heterodimeric proteins capable of forming quaternary structure as a mature protein is nowhere addressed in Andreansky and rather is only found in the instant application. Additionally, the differential in IL-12 gene expression rates between Toda and the claimed invention necessitates a change in promoter, as well as predominant mechanism of activity from extensive lysis per Toda, as compared to the claimed invention. Taking these factors together, it is submitted that these parameters have to be varied or alternatively each of numerous possible choices would have to be made until one arrived at a successful result. Since the prior art gives neither an indication of which parameters are critical nor direction as to which of many possible choices is likely to be successful, it is submitted that in light of the above discussion, the amount of work required to arrive at the claimed invention from the prior art reference combination is considerable to an extent that would dissuade one skilled in the art from performing the prior art reference combination as advocated in the outstanding Office Action.

In light of the above remarks, withdrawal of the rejection as to claims 1, 2, 5-9 and 12-16 under 35 U.S.C. §103(a) over Andreansky et al. in view of Toda et al. is solicited.

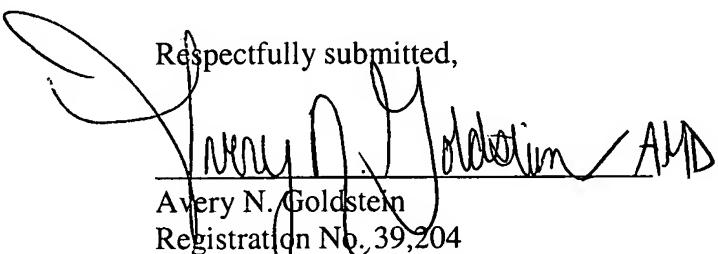
Summary

Claims 1, 2, 5-9, 12-18 and 20-26 are the claims pending in this application. Claims 17, 18 and 20-23 have been amended consistent with language found in the outstanding Office Action under the heading “Allowable Subject Matter.” As such, claims 17, 18 and 20-23 are now believed to be in allowable form. Claims 3, 4, 10, 11 and 19 have been canceled by way of this amendment. New claims 24-26 have been added. With the entry of this amendment, all the

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pending claims are now believed to be in allowable form and directed to patentable subject matter. Reconsideration of the outstanding rejections and allowance of the pending claims is solicited. Should the Examiner have any suggestions with respect to the pending claims, he is kindly requested to contact the undersigned attorney in charge of this application to resolve any outstanding issues.

Respectfully submitted,


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Enclosures

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DATE OF DEPOSIT February 17, 2004

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